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Comparison of cardiac output estimates by echocardiography and bioreactance at rest and peak dobutamine stress test in heart failure patients with preserved ejection fraction

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Abstract

Purpose: To assess the agreement between cardiac output estimated by two dimensional echocardiography and bioreactance methods at rest and during dobutamine stress test in heart failure patients with preserved left ventricular ejection fraction (HFpEF).

Methods: Haemodynamic measurements were assessed in 20 stable HFpEF patients (12 females; aged 61 ± 7 years) using echocardiography and bioreactance methods during rest and dobutamine stress test at increment dosages of 5,10,15 and 20 $\mu\text{g}/\text{kg}/\text{min}$ until maximal dose was achieved or symptoms and sign occurred i.e. chest pain, abnormal blood pressure elevation, breathlessness, ischemic changes, or arrhythmia.

Results: Resting cardiac output and cardiac index estimated by bioreactance and echocardiography were not significantly different. At peak dobutamine stress test cardiac output and cardiac index estimated by echocardiography and bioreactance were significantly different (7.06 ± 1.43 vs 5.71 ± 1.59 L/min, $p < 0.01$; and 4.27 ± 0.67 vs 3.43 ± 0.87 L/m²/min; $p < 0.01$) due to the significant differences in stroke volume. There was a strong positive relationship between cardiac outputs obtained by the two methods at peak dobutamine stress ($r = 0.79$, $p < 0.01$). The mean difference (lower and upper limits of agreement) between bioreactance and echocardiography cardiac outputs at rest and peak dobutamine stress were -0.45 (1.71 to -2.62) L/min and -1.35 (0.60 to -3.31) L/min respectively.

Conclusion: Bioreactance and echocardiography methods provide different cardiac output values at rest and during stress thus cannot be used interchangeably. Ability to continuously monitor key haemodynamic variables such as cardiac output, stroke volume and heart rate is the major advantage of bioreactance method.

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome associated with poor prognosis; increased mortality and hospitalization and reduced quality of life and functional independence [1, 2]. HFpEF is characterised by clinical signs of heart failure with left ventricular ejection fraction (LVEF) over 50% [3]. The heterogeneity of HFpEF syndrome makes its diagnosis and treatment challenging. HFpEF is a slowly progressive multifactorial clinical syndrome where there is a close interaction of aging and co-morbidities with cardiovascular and systemic mechanism resulting in clinical symptoms characterised by low functional reserve and reduced cardiac performance. Recently, there has been a growing interest about knowledge of cardiac output and cardiac performance both at rest and after stress in patients of HFpEF. Computation of LVEF involves cardiac stroke volume which in turn affects the cardiac output. Cardiac output, defined as the amount of blood volume the heart pumps through the systemic circulation over a period measured in liters per minute[4], is an important measure of cardiac performance providing an indication of systemic oxygen delivery and global tissue perfusion [5, 6]. The average cardiac output for a healthy adult is approximately 5–6 l /min [5], increasing four-folds in untrained individuals, and up to sevenfold in trained athletes [7].

Optimal strategy to diagnose HFpEF should incorporate haemodynamic evaluation at rest and in response to stress-induced increase in filling pressures [3]. In patients with heart failure, cardiac power output obtained during stress testing, either by physiological or pharmacological stimulations, coupled with blood pressure, is the strongest predictor of mortality and functional capacity [8, 9].

Since the discovery of invasive cardiac output measurement by Adolf Fick in 1870[10], and the subsequent introduction a century later, of the Swan Ganz pulmonary artery catheterisation based on bolus thermodilution [11], other newer minimally invasive and non-invasive techniques have been discovered. These newer techniques are such as pulse contour analysis, oesophageal doppler, inert gas rebreathing, thoracic bioimpedance, thoracic bioreactance and echo doppler method [12] limit risks associated with infections, arrhythmia, complications of central line insertion and also cost.[5, 13].

However, their acceptability has been limited by inaccuracy and unreliability [12, 14]. An ideal cardiac output monitor should be easy to use, valid, reliable, reproducible, non-invasive, cheap with fast response time [12, 15]. Recently there has been a lot of clinical and research focus on two dimensional echocardiography and bioimpedance derived cardiac output monitoring in various clinical scenarios [16-18].

Echocardiography has emerged as an important tool in the diagnosis, management and prognostication of patients of heart failure and is the most utilized non-invasive tool in clinical and research settings [19, 20]. 2-Dimensional (2D) echocardiography is regularly used for the assessment of cardiac output in various clinical settings especially in critical care settings and in cardiology. It has been extensively validated against the gold standard thermodilution technique both at rest and after exercise [21, 22]. The bioimpedance derived cardiac output method has been validated with the invasive gold standard method of thermodilution for assessing cardiac output [23]. Previous reports have also shown that bioimpedance demonstrated acceptable test-retest reliability for estimating cardiac output and stroke volume at rest and after physiological stress test in healthy individuals [24]. Although bioimpedance and 2D echocardiography have been widely studied, no studies have compared both techniques directly. Therefore, the aims of the present study are (1) to compare resting and dobutamine induced stress bioimpedance and echocardiography derived cardiac outputs in stable patients of HFpEF and (2) to assess the agreement between the bioimpedance and 2D echocardiography methods.

Methods

This was a single centre, prospective observational, direct comparison study between bioimpedance and transthoracic echocardiography methods for measuring cardiac output at rest and at peak stress.

Participants

Twenty stable HFpEF patients (12 females and 8 males) participated in the study, which was conducted at the Sengupta Hospital and Research Institute, Ravinagar, Nagpur, India. Ethical approval for this study was provided by an Independent Research Ethics Committee affiliated to hospital. Clinically stable HFpEF patients who were willing to give informed consent and also visit the clinical research facility were included in the study. Patients having valvular heart

disease, cardiac arrhythmias, myocardial infarction, percutaneous coronary intervention and/or bypass graft surgery over the past 3 months, primary pulmonary hypertension and active malignancy were excluded from the study. Subjects were instructed to abstain from eating for at least 2 hours before the test and from vigorous exercise 24 h prior to the test. Subjects were also instructed not to consume alcohol or caffeine containing foods and beverages on test days. Upon arrival at the laboratory, participants were informed of the benefits and potential risks of the study and they subsequently provided a written informed consent. Participants were asked to lay in a supine position for 10 min. Blood pressure was measured in duplicate in the brachial artery of participant's non-dominant arm.

Study protocol and measurements

Heart rate, stroke volume, cardiac output and cardiac index were recorded using bioreactance and transthoracic echocardiography simultaneously at rest and at peak dobutamine infusion stress test with incremental dose of 5,10,15, and 20 ug/Kg/min in 3 minutes stages. The test was terminated when the participant achieved the targeted dose of dobutamine infusion, or symptoms and signs i.e. breathlessness and palpitation were present, or patient desired to stop assessment for any reason. Atropine injection was not used in the protocol.

Bioreactance

The bioreactance system used in this study was NICOM (Cheetah Medical, Delaware, USA). NICOM provides cardiac output monitoring non-invasively and uses time-dependent relative phase shifts of an oscillating current traversing the thoracic cavity [23]. The NICOM system uses a radiofrequency generator that creates a high-frequency current injected across the thorax. These currents are passed through four dual-surface electrodes which are attached over the trapezius muscle on either side of the upper body and lower posterior torso lateral to the margin of the latissimus dorsi musculature. The signals are passed through these electrodes and recorded back and then processed digitally. The signal processing unit of the system determines the relative phase shift between the input signals relative to the output signals. This phase shift is due to instantaneous changes in blood flow in the aorta. Cardiac output (QT) is subsequently calculated by:

$$QT = \frac{1}{4} \delta C VET DU = dt_{max} P HR$$

where C is a constant of proportionality, and VET is ventricular ejection time, which is

determined from the bioreactance and electrocardiogram signals, $D\Phi/dt_{\max}$ is the relative phase shift of current, and HR is heart rate. The value of C has been optimized in prior studies and is dependent on patient's age, gender and body size.

Transthoracic echocardiography

Transthoracic echocardiography (TE) was performed using a commercially available echocardiographic system, Vivid E95 (General Electric Company, Vingmed Ultrasound AS, Horten, Norway). A single experienced operator performed all the data acquisitions. Images were obtained in the parasternal short-axis view at 3 left ventricular (LV) levels: basal, mid, and apical, and in apical 4-, 3-, and 2-chamber views, with images taken at rest and at peak dobutamine infusion. An average of three beats were captured for analysis. Echocardiographic assessment was done at 50-70 frame rate/seconds. A 17-segment model of the LV was used for analysis. In parasternal long axis view, the LV out flow tract measurement was taken in the phase of systole according to the chamber guidelines. Pulsed-wave doppler of the LV out flow tract was recorded from either apical five-chamber or long-axis view depending on best alignment of the doppler beam to flow direction. The stroke distance was measured by tracing of the flow profile which produces the velocity time integral (VTI). Stroke volume was then calculated by the formula:

Stroke volume = (LVOT diameter)² x 0.785 X LVOT VTI, where LVOT is left ventricular outflow tract [25-27].

Cardiac output and cardiac index were calculated by the formulae:

Cardiac output (L/min) = Stroke volume (ml/beat) x heart rate (beats/min)

Cardiac index (L/min/m²) = Cardiac output (L/min) / body surface area (m²)

Dobutamine stress test

Dobutamine stress test (DSE) was performed using the protocol previously defined.[18] Dobutamine was administered by a peripheral intravenous line without any foreseeable side effects in a medically controlled environment. Before the test, patients were asked to stop any beta-blocker drug or nitrates, 24 hours prior to the test. Patients were asked to fast for 4 hours

prior to the test. Dobutamine was infused intravenously in 3-minute intervals, with gradual dose titration from 5,10,15 and 20 µg/kg/min until maximal dose was achieved or symptoms and sign occurred i.e. chest pain, abnormal blood pressure elevation, breathlessness, ischaemic changes, arrhythmia or patients ability to tolerate the drug. All the standard echocardiographic views were taken before starting the DSE and at the time of peak tolerated dose.

Statistical analysis

Data are expressed as mean (\pm SD) unless otherwise stated. Normality of distribution was evaluated using a Kolmogorov– Smirnov test. Independent t test was used to determine significance between the bioreactance and dobutamine stress echocardiography. Paired samples t-test was used to assess differences between the two methods at rest and peak dobutamine stress. To assess the relationship between the two methods Pearson's or Spearman's coefficient of correlation was used as appropriate. Bland–Altman plots were constructed to evaluate the mean difference and upper and lower limits of agreements (± 2 SD of mean difference) between bioreactance and echocardiography methods. All statistical analysis was carried out using SPSS version 20 (SPSS Inc., Chicago, IL, USA) and R-3.0.0 programming tool (IBM, Chicago,IL:60606, USA) Data are expressed as mean \pm SD unless otherwise stated and statistical significance was indicated if $p < 0.05$.

Results

Participants were aged 61 ± 7 years, weight 67 ± 15 kg, height 154 ± 7 cm and body surface area 1.66 ± 0.19 m². The baseline parameters of the patient population are summarized in Table 1. The NT- proBNP levels of the patient population was 960 ± 1129 pg/ml. In all subjects a stable bioreactance signal was obtained at rest and throughout the dobutamine stress test. Resting heart rate estimated by bioreactance and 3-lead ECG accompanying echocardiography were not significantly different. The average dose of dobutamine for all the participants was 18.75 ± 2.22 ug/kg/min. There was no significant difference in resting cardiac output and cardiac index estimated by bioreactance and echocardiography (Table 2). There was a moderate positive relationship between bioreactance and echocardiography derived cardiac output at rest ($r=0.56$, $p < 0.01$; Figure 1).

At peak dobutamine stress, there was no significant difference in heart rate. However, bioreactance reported significantly lower cardiac output values compared to Doppler

echocardiography ($p < 0.001$, Table 2). There was a strong positive relationship between bioreactance and echocardiography derived cardiac outputs at peak dobutamine stress ($r = 0.79$, $p < 0.001$; Figure 1).

The mean difference (lower and upper limits of agreement) between bioreactance and echocardiography cardiac outputs at rest and peak dobutamine stress was -0.45 (1.71 to -2.62) L/min and -1.35 (0.60 to -3.31) L/min respectively (Figure 2A,2B). For stroke volume, the mean difference (with upper and lower limits of agreement) between the two methods at rest and peak dobutamine stress was -5.69 (19.8 to -31.2) ml/beat and -9.2 (9.59 to -27.99) ml/beat respectively.

Discussion

The present study compared two non-invasive methods for estimating cardiac output i.e. echocardiography and bioreactance at rest and after dobutamine stress test in stable patients with HFpEF. This is the first study to investigate non-invasive hemodynamic monitoring using both methods. . The important finding of the *study* is that at rest, both echocardiography and bioreactance derived cardiac output and stroke volume were similar. At peak dobutamine stress, bioreactance recorded lower cardiac output compared to echocardiography. However, the calculated limits of agreement were wide and unacceptable, suggesting that the two methods cannot be used interchangeably both at rest and peak stress.

The usage of bioreactance technique for cardiac output assessment during rest and after exercise has been earlier evaluated in chronic heart failure patients[28, 29] . In a recent study, Rali et al. showed that the NICOM technology is not a reliable method for measuring cardiac output in patients with decompensated heart failure and cardiogenic shock when compared with indirect Fick's thermodilution method[30]. The authors explained that bioreactance method is dependent on oscillation of electric current which passes through the thoracic cavity and in patients with advanced heart failure, pulmonary and interstitial edema affects the passage of these signals. Also alteration in right sided and left sided preload seen in heart failure patients affect the intrathoracic impedance which in turn impacts the current phase shifts necessary to calculate SV and CO. However studies have also shown that bioreactance is useful in evaluation of fluid responsiveness in critical care settings [31]. This may be important in clinical scenario like in HFpEF patients where fluid hemodynamics and filling pressures assessment are important in patient management.

Echocardiography is a useful, and reliable method for estimating cardiac output in critically ill patients [21]. In a cohort of 38 mechanically ventilated patients, Mercado et al. showed that echocardiography derived cardiac output correlated well with invasive swan-Ganz derived cardiac output [21]. They used the pulse wave **doppler** of aortic blood flow in apical five-chamber view to calculate cardiac output similar to the present study. Various studies have shown that that cardiac output derived from aortic blood flow by pulse wave doppler using apical five chamber view was better than that derived from signals from pulmonary or mitral valves [32, 33]. Also in our study, we used the left ventricular out flow tract velocity time integral from echo to derive cardiac output. This method has been better than ejection fraction derived cardiac output in patients with advanced heart failure for prediction of outcomes [34]. However, the accuracy of echo derived cardiac output is limited by errors in determining cross sectional area of LVOT[34]. So a careful assessment of LVOT cross sectional area is mandatory.

At peak dobutamine stress, there was no interference in signals and no artifacts seen in our study. Both cardiac output methods used in the study were non-invasive and easy to operate. Bioreactance provides continuous cardiac output monitoring, is patient friendly and does not require a familiarization procedure and may have wider application, especially in cardiology settings where cardiac output monitoring is important. However the only challenge can be in patients who have implanted cardiac device as it may interfere with the signals [35]. Also, bioreactance cardiac output is based on the assumption that the area under the flow pulse is proportional to the product of peak flow and ventricular ejection time. So in conditions of low flow status, the readings may have low accuracy[36].

The present study has few limitations. First, the gold standard Fick's method of assessment of cardiac output was not included. Fick's principle involves invasive procedure associated with complications as discussed earlier which may not be suitable in HFpEF patients. **Applying the gold standard of Fick's method to this study could have raised ethical concerns as there would have been increased risk to the study's population due to its invasive nature. However, both techniques have been previously validated against the invasive gold standard methods, that is thermo-dilution and Fick's techniques. Results revealed acceptable levels of agreement between bioreactance and echocardiography with these invasive methods.(21-23)** Second, this is a single centre study with a small sample size. However, this is the first study showing the usage of two non-invasive methods for assessing cardiac output during rest and

pharmacological stress in patients with HFpEF.

In conclusion, bioreactance and echocardiography provide different cardiac output estimates, especially at pharmacological stress exercise, therefore cannot be used interchangeably in patients with HFpEF. Technological differences, alteration in loading conditions, complex haemodynamics of HFpEF and changes in pulmonary vascular reserve seen in HFpEF are likely to explain discrepancies in cardiac output estimates between the bioreactance and echocardiography derived cardiac outputs. Future studies are warranted to assess performance of bioreactance and echocardiography against the gold standard procedure in various cardiac conditions.

This is the first study to compare cardiac output by echocardiography and bioreactance at rest and at peak dobutamine stress test in patients of HFpEF. Both these methods are non-invasive, easily available and could potentially be used in wider clinical practice in cardiology where the use of gold standard invasive methods is not viable. This is particularly important in clinical settings where it is necessary to estimate the haemodynamic response to a physiological or pharmacological challenge, such as fluid responsiveness, passive leg raising, surgery, drug titration, and anaesthesia. The present findings suggest that echocardiography cannot be used interchangeably with bioreactance. However, this should not preclude its use in clinical practice, where its advantages over the gold-standard methods have been well documented and its reliability in challenging haemodynamic scenarios has been confirmed.

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Table 1. Patient demographic and clinical characteristics.

<i>Demographics</i>	Mean \pm SD
Age (years)	61 \pm 7
Height (cm)	154 \pm 7
Weight (Kg)	67 \pm 15
Body surface area (m ²)	1.66 \pm 0.19
<i>Clinical Characteristics</i>	
NYHA class	1.3 \pm 0.47
Left ventricular ejection fraction (%)	54.45 \pm 3.03
Hypertension (%)	85
Diabetes mellitus (%)	35
Ischaemic heart disease (%)	20
ACEI/ARBs (%)	80
Beta blocker (%)	30
Diuretics (%)	35
Calcium channel blockers (%)	10

NYHA – New York Heart Association functional class; ACE- Angiotensin converting enzyme inhibitor, ARB- Angiotensin receptor blockade.

Table 2: Comparison of echocardiography and bioreactance measurements rest and peak dobutamine stress test.

	Echocardiography	Bioreactance	P value
<i>Rest</i>			
Heart rate (beats/min)	78± 15	78± 16	0.93
Cardiac output (L/min)	4.61± 1.09	4.15± 1.23	0.07
Cardiac index (L/m ² /min)	2.80± 0.76	2.49± 0.61	0.08
Stroke volume (ml)	59.48± 11.88	53.78± 13.86	0.06
Systolic Blood pressure (mm Hg)	121.33± 8.34	117.87± 17.61	0.29
Diastolic Blood pressure (mm Hg)	76.67± 4.88	69.33± 10.06	< 0.01
<i>Peak stress test</i>			
Heart rate (beats/min)	103± 15	102± 16	0.54
Cardiac output (L/min)	7.06± 1.43	5.71± 1.59	< 0.01
Cardiac index (L/m ² /min)	4.27± 0.67	3.43± 0.87	< 0.01
Stroke volume (ml)	67.77± 15.66	58.57± 21.22	< 0.01
Systolic Blood pressure (mmHg)	136.60± 23.43	125.47± 42.13	0.54
Diastolic Blood pressure (mm Hg)	78.67± 9.15	71.53± 10.41	< 0.01

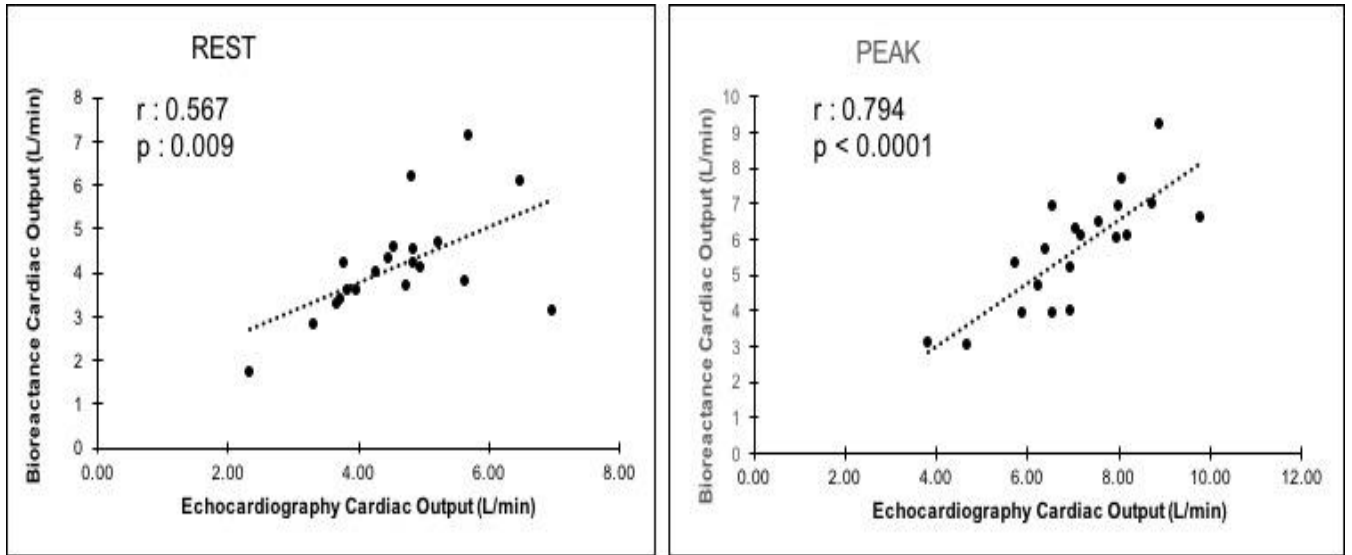


Figure 1: Relationship between echocardiography and bioreactance cardiac outputs at rest and peak dobutamine stress

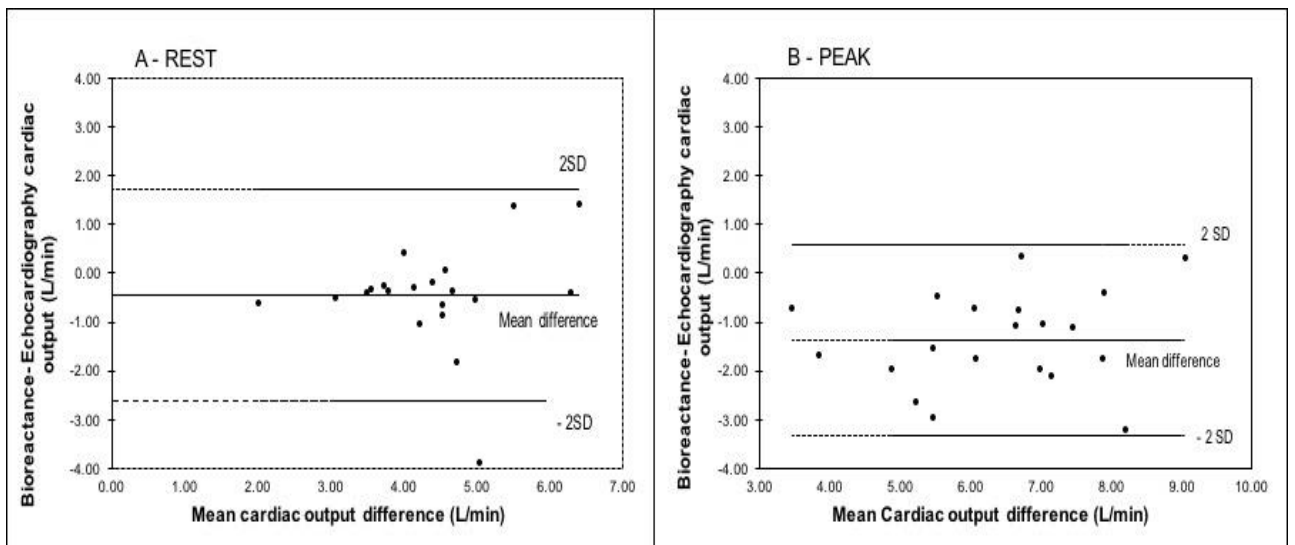


Figure 2: Bland-Altman plot to demonstrate mean difference and upper and lower limits of agreement between bioreactance and echocardiography derived cardiac outputs measured at rest (A) and peak dobutamine stress test (B).